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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/526,369	03/03/2005	Iwao Katsuyama	1422-0666PUS1	6217

2292 7590 09/24/2007

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EXAMINER	
ARCHIE, NINA	
ART UNIT	**PAPER NUMBER**
1645	

NOTIFICATION DATE	DELIVERY MODE
09/24/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/526,369	KATSUYAMA ET AL.	
	Examiner	Art Unit	
	Nina A. Archie	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 May 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5 and 7-28* is/are pending in the application.

4a) Of the above claim(s) *7-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,19-22 and 25* is/are rejected.

7)☐ Claim(s) *23-24 and 26-28* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This Office is responsive to Applicant's amendment and response filed 5-29-07. Claims 1-5 have been amended. Claim 6 has been cancelled. Claims 7-18 are withdrawn. Claims 19-28 are new claims.

Information Disclosure Statement

2. The information disclosure statement filed July 3, 2006 has been considered. An initialed copy is enclosed.

The legible copies of each document of the IDS of March 3, 2005 and July 15, 2005 have not been receiver. Examiner request that Applicant send legible copies of each document of the IDS filed on March 3, 2005 and July 15, 2005.

Objections/Rejections Withdrawn

3. A) Rejection of only claims 1-6 listed below under 35 U.S.C. 112, second paragraph, page 6 paragraph 2 is withdrawn in light of cancellation of the claim 6 and in light of applicant's amendment thereto.

As to claim 1, the phrase ' wherein the transformed yeast is capable of expressing a heterogeneous protein'; the term capable renders the claims indefinite as it is not clear whether the heterogeneous protein is expressed or not. Applicant(s) can modify claim to recite 'wherein the transformed yeast expresses the heterogeneous protein' provided there is support for such modification in the specification as instantly filed.

As to claim 5, the phrase aspiration in "yeast is deficient in aspiration ability" is confusing in light of the dictionary definition of 'aspiration'. Aspiration is defined in the American Heritage Dictionary (see attached) as 'expulsion of breath in speech', 'the act of breathing in; inhalation' or 'the process of removing fluids or gases from the body with a suction device'. Does applicant mean, for example, that the yeast is deficient in inhalation or is the yeast is deficient in removing fluids or gases from its cell? The term

used in the art for such yeast as described on page 25 lines 15-20 of the specification is respiration deficient yeast and not aspiration deficient yeast. Applicants should specifically clarify the metes and bounds of this term.

As to the phrase 'shows a change in a growing state', its not clear what growing state the claim is referring to. For example, if the growing state (of the transformed yeast) is lowered, can the test sample further lower the growing state?

As to claim 6, the term "change" in claim 5 is a relative term, which renders the claim indefinite. The term "change" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably appraised of the scope of the invention. The claim is not clear as to the basis of comparison for measuring ' a change'. In addition, the phrases ' a change in wet-weight of the yeast' and ' a change in dry-weight of the yeast' is confusing. Does applicant mean to measure the wet-weight or dry- weight of a single yeast cell? Appropriate correction is needed to clarify the claim provided there is support for said clarifications in the specification.

b) Rejection of claims 1-5 under U.S.C. 102(b), pages 8-13 is withdrawn in light of applicant's amendment.

Claim Rejections Maintained

35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly

connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

4. The rejection of Claims 1-6 under 35 U.S.C. 112 first paragraph is maintained for the reasons set for in the previous office action.

Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application filed, had possession of the claimed invention.

Applicant arguments:

A) Applicants point out that claim 6 has been canceled and claims 1-5 have been amended so that they do not recite the "heterogeneous protein" limitation.

Applicants state that new claim 19, however, does recite the "heterogeneous protein" limitation. Here, Applicants point out that a patent need not teach, and preferably omits, what is well known in the art. In re Buchner, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991). With these points in mind, Applicants direct the Examiner's attention to the fact that the claims specify that the heterogeneous proteins control cell proliferation or regulate cell cycle control. Applicants submit that the classes of proteins that control cell proliferation and regulate cell cycle are well known in the biotechnology field.

In further support of Applicants' position, Applicants direct the Examiner's attention to the following exemplary and non-exhaustive list of publications discussed in the Applicants Remarks on 5/29/2007. Applicants submit that these publications, together with a myriad of other publications not listed by Applicants in the interest of efficiency, demonstrate that the identity of individual proteins, which comprise the presently claimed heterogeneous protein genus, are known in the art. In addition, Applicants point out that these publications disclose the exact primary amino acid sequences, three dimensional protein crystal structures and co-crystal structures for a substantial number of the members of the presently claimed heterogeneous protein genus.

Applicants also point out that the specification describes members of the presently claimed heterogeneous cell differentiation control and cell cycle regulator proteins that the Examiner simply ignores in imposing the written description rejection. Namely, the Specification describes Tob and Caf family proteins as members of the presently claimed heterogeneous proteins (see for example page 5 line 12 - page 7, line 10 of the Specification), and documents their reduction to practice in the screening method of the invention, both independently and simultaneously, in the Examples. Moreover, the exact amino acid sequences of the domains of import to the function of Tob and Caf proteins are set forth in the Sequence Listing and on pages 14-17 of the Specification. Applicants submit that this disclosure provides structure-function correlation, to which the Examiner fails to give proper evidentiary weight by simply not

taking it into consideration in imposing the written description rejection.

Examiner's Response to Applicant's Arguments:

A) Examiner accepts that claim 6 has been canceled and claims 1-5 have been amended so that they do not recite the "heterogeneous protein" limitation. Examiner accepts that Applicants state that new claim 19, however, does recite the "heterogeneous protein" limitation. However claims 1-6 are rejected under USC 112 first paragraph in the Office Action on 12/6/2006. Examiner accepts that the Applicant has submitted publications, together with a myriad of other publications not listed by Applicants in the interest of efficiency, demonstrate that the identity of individual proteins which comprise the presently claimed heterogeneous protein genus are known in the art. In addition, Applicants point out that these publications disclose the exact primary amino acid sequences, three dimensional protein crystal structures and co-crystal structures for a substantial number of the members of the presently claimed heterogeneous protein genus.

Examiner disagrees that Applicants have describe members of the presently claimed heterogeneous cell differentiation control and cell cycle regulator proteins. Applicant state that Tob and Caf family proteins as members of the presently claimed heterogeneous proteins or those having a function of inhibiting or enhancing function may serve as a prophylactic agent and/or therapeutic agent for various diseases involved in proliferation or differentiation of cells (see for example page 5 line 12 - page 7, line 10 of the Specification). Applicant disclose that amino acid sequences of the domains of import to the function of Tob and Caf proteins are set forth in the Sequence Listing and on pages 14-17 of the Specification.

The specification does not provide any definition or guidance as to the structural, physical or chemical characteristics of a heterogeneous protein. The specification only defines heterogeneous protein functionally as 'a protein for an yeast capable of inducing a change in the growing state of an yeast' and 'the heterogeneous protein includes a fragment of the protein as long as the fragment has a similar function to that of the

protein' (specification page 10 last bridging paragraph, page 11 lines 1-2, page 13 lines 11-12). The genus of heterogeneous proteins is vast and encompass many different proteins and fragments of proteins potentially having different functions (for example, kinases, phosphatases, helicases, DNAses, transcriptases, proteases) and which are unrelated by structure and the disclosure fails to adequately define the common structural attributes of the genus of heterogeneous proteins that have the related function. Mere function does not describe a structure, because the specification does not provide relevant identifying characteristics, including a known disclosed correlation between function and structure. The courts have held that in these instances, the specification lacks written description see Enzo Biochem Inc. v. Gen-Probe Inc. 63 USPQD2D 1609 (CAFC 2002) and University of Rochester v. G. D. Searle & Co. 69 USPQ2D 1886 (CAFC 2004). When the genus is vast and compounds (in this case - heterogeneous proteins) are claimed by function alone and the specification lacks a known or disclosed correlation between structure and function, the written description of the specification does not convey possession of the claimed genus.

Therefore one of skill in the art would reasonably conclude that the disclosure of accession numbers (specification page 22) as examples of genes encoding a heterogeneous protein fails to provide a representative number of species to describe the claimed genus of heterogeneous proteins. Also, the disclosure of the sequence of a protein belonging to the Tob and Caf family and identification of regions amino acid homology in the Tob and Caf family fails to provide a representative number of species to describe the vast and varied genus of heterogeneous proteins as instantly claimed (specification page 14 lines 17 to page 17).

Therefore this disclosure fails to meet the written description limitation of structure-function correlation.

Claim Rejections Maintained

35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Prior to the below rejections: the term used in the art for the yeast described on page 25 lines 15-26 of the specification is respiration deficient yeast and not aspiration deficient yeast. The examiner has therefore interpreted yeast deficient in aspiration ability to mean yeast deficient in respiration ability for prior art purposes.

5. The rejection of claims 1-6 under 35 U.S.C. 103(a) is maintained for the reasons set for in the previous office action.

Applicant arguments:

A) Applicants have canceled claim 6 and amended claims 1-5. Applicants point out that, with the exception of Nakahama et al. (1993), the prior art references relied on by the Examiner in imposing the obviousness rejections are the same as the those relied on by the Examiner in imposing the anticipation rejections, which fail to teach all aspects of the currently claimed screening method as pointed out by Applicants in traversal of the anticipation rejection. Applicants submit that the Nakahama et al. (1993) reference fails to rescue the deficiencies common to Bounaga et al., Superti-ferga et al., Florio et al. and Perkins et al.; so even the combination of the prior art references of record fail to teach the presently claimed invention. The Examiner has therefore failed to establish a prima fascie case of obviousness, and the obviousness rejections are improper. Accordingly, Applicants respectfully request reconsideration and withdrawal of all of the obviousness rejections. Applicants have enclosed a Declaration of Dr. Masao Tokunaga.

Examiner's Response to Applicant's Arguments:

Examiner disagrees that Applicants submit that the Nakahama et al. (1993) reference fails to rescue the deficiencies common to Bounaga et al., Superti-ferga et al., Florio et al. and Perkins et al.; so even the combination of the prior art references of record fail to teach the presently claimed invention. The Examiner disagrees that the obviousness rejections are improper.

Bounaga et al teach a method for screening and identification of compounds or compositions useful as herbicides, growth regulators or fungicides comprising (1) addition of a compound or composition to be screened or identified to a culture or culture area of a yeast strain transformed with and expressing one or more plant or animal or human cell cycle control genes or mutants thereof as well as to a control yeast strain; and (2) determining the effect on the phenotype such as inhibition or stimulation of growth and/or cell division and/or changing cell shape and size of said transformed yeast compared to said control yeast (page 4 lines 1-9, page 7 line 21, page 12 lines 30-34). Bounaga et al teach that the transformed yeast expresses a cell cycle control gene resulting in growth arrest or growth acceleration (page 30 claims 7 and 8) and said cell cycle control gene is involved in regulation of cell cycle of a mammal (page 12 lines 30-34), for example, involved in control of entry (that is from GO/G1 phase) and progression through S phase of the cell cycle (page 5 lines 9-10) such as cyclin dependent kinases (CDK), cyclin dependent kinase inhibitor, cyclin A, D, E etc (page 5 line 1-9 and lines 10-34 and page 6 lines 1-9). Bounaga et al teach methods of testing effect of compounds or compositions on growth of yeast (page 15 lines 27-34) by measuring shape, size, number, growth rate, growth stimulation or growth inhibition, phenotype, turbidity (page 16 lines 4-13).

Bounaga et al does not teach a method of Screening wherein the transformed yeast is deficient in aspiration ability. Nakahama et al teach transformation of respiration deficient yeast. Nakahama teach that respiratory deficient strains of yeast transformed with expression plasmids of genes provide higher gene expression than their parent strains (i.e. non-respiratory deficient yeast) and that the gene expression is increased by rendering the yeast respiratory deficient (see abstract and column 2 lines 3141). Therefore one would have been motivated at the time of the invention to use a

respiratory deficient yeast for transformation and expression of genes in the method of screening of Bounaga et al as taught by Nakahama et al because Nakahama teach that respiratory deficient strains of yeast transformed with expression plasmids of genes provide higher gene expression that their parent strains and provide a higher amount of expressed protein.

Superti-furga et al teach a screen for regulators and antagonizers of protein tyrosine kinases comprising (1) transforming yeast cells c-Src under conditions which expression of c-Src can be induced (2) transforming (contacting) said transformed yeast with a vector comprising a cDNA library from fibroblasts or B-cells under a constitutive promoter (3) and then measuring whether said transformed yeast is able to grow when c-Src expression is induced (page 600 first paragraph under results section and figure 1). Superti-furga et al teach that c-Src (human and chicken) expression in transformed yeast cells causes growth inhibition (figure 4a and b). c-Src is a protein involved in regulating cell cycle of a mammal cell and is involved in intracellular signaling of GO/G1 phase of a mammalian cell. Superti-furga teach that the growing state of the transformed yeast is determined by a morphological change i.e. the ability of cells to form colonies (page 601 column 2 fig 1).

Superti-furga et al does not teach a method of screening wherein the transformed yeast is deficient in aspiration ability. Nakahama et al teach transformation of respiration deficient yeast. Nakahama teach that respiratory deficient strains of yeast transformed with expression plasmids of genes provide higher gene expression than their parent strains (i.e. non-respiratory deficient yeast) and that the gene expression is increased by rendering the yeast respiratory deficient (see abstract and column 2 lines 31-41). Therefore one would have been motivated at the time of the invention to use a respiratory deficient yeast for transformation and expression of genes in the method of screening of Superti-furga et al as taught by Nakahama et al because Nakahama teach that respiratory deficient strains of yeast transformed with expression plasmids of genes provide higher gene expression that their parent strains and provide a higher amount of expressed protein.

Florio et al teach (1) transformed yeast expressing v-src wherein said expressed v-src lowers the growth of said transformed yeast (p 287 fig. 1) (2) coexpressing (contacting) human phosphotryosylphosphatase (hPTPIB)in said transformed yeast (p.289 fig.5C) (3) and measuring the growing state of the yeast. Florio et al teach that expression of v-src in yeast cells lowers the growth of yeast and that coexpression with hPTP1B reverses growth inhibition of v-src (p 289 fig.5C). Florio et al teach growth of said transformed yeast cells was monitored by measuring a change in the absorbance of the yeast culture (i.e. turbidity) at A600nm (P 289 fig 5C). V-src is a protein involved in regulating cell cycle of a mammal cell and is involved in intracellular signaling of the GO/G1 to S phase (i.e. quiescent cell entry into S phase) of the cell cycle (see ender citation of relevant art Riley et al 2001 Oncogene vol. 20 p. 5941-5950).

Florio et al does not teach a method of screening wherein the transformed yeast is deficient in aspiration ability. Nakahama et al teach transformation of respiration deficient yeast. Nakahama et al teach that respiratory deficient strains of yeast transformed with expression plasmids of genes provide higher gene expression than their parent strains (i.e. non-respiratory deficient yeast) and that the gene expression is increased by rendering the yeast respiratory deficient (see abstract and column 2 lines 31-41). Therefore one would have been motivated at the time of the invention to use a respiratory deficient yeast for transformation and expression of genes in the method of screening of Florio et al as taught by Nakahama et al because Nakahama teach that respiratory deficient strains of yeast transformed with expression plasmids of genes provide higher gene expression that their parent strains and provide a higher amount of expressed protein.

Perkins et al teach a method of screening of inhibitors of poly(ADP-ribose) Polymerase/PARP1 and PARP2 comprising contacting a yeast transformed and expressing PARP1 and PARP2 (p. 4177 fig.I) with chemical compounds (p. 4178 fig. 3, p.4179 fig. 5). Perkins et al teach that expression of PARP1 or PARP2 in said yeast causes growth inhibition (p. 4177 fig. 1) and that said chemical compounds reverse growth inhibition caused by PARP1 expression in said yeast (p. 4178 fig.3). Perkins et

al teach growth of said transformed yeast cells was monitored by measuring a change in the absorbance of the yeast culture (i.e. turbidity) at As00nm (P. 4177 column 2 second full paragraph).

Perkins et al does not teach a method of screening wherein the transformed yeast is deficient in aspiration ability. Nakahama et al teach transformation of respiration deficient yeast. Nakahama teach that respiratory deficient strains of yeast transformed with expression plasmids of genes provide higher gene expression than their parent strains (i.e. non-respiratory deficient yeast) and that the gene expression is increased by rendering the yeast respiratory deficient (see abstract and column 2 lines 31-41). Therefore one would have been motivated at the time of the invention to use a respiratory deficient yeast for transformation and expression of genes in the method of screening of Perkins et al as taught by Nakahama et al because Nakahama teach that respiratory deficient strains of yeast transformed with expression plasmids of genes provide higher gene expression that their parent strains and provide a higher amount of expressed protein.

Examiner accepts the declaration that Applicants have enclosed by Dr. Masao Tokunaga. However the declaration is not persuasive. Applicant's declaration explaining the claimed invention is not found in claims 1-5.

As outlined previously, the instant claims are to drawn to (claim 1) a method of screening a physiologically active substance, comprising the steps of: (1) contacting a transformed yeast with a test sample, wherein the transformed yeast is capable of expressing a heterogeneous protein, and shows a change in a growing state in an expression state of the protein as compared to that in a non-expression state of the protein; (2) culturing the yeast under conditions that the protein is capable of being expressed; and (3) measuring the growing state of the yeast, wherein the physiologically active substance is judged to be present in the test sample in a case where the growth of the yeast is lowered or improved in the presence of the test sample as compared to that in the absence of the test sample as a control. (claim

6) wherein the transformed yeast is deficient in aspiration ability.

Bounaga et al is set forth supra. Bounaga et al does not teach a method of Screening wherein the transformed yeast is deficient in aspiration ability. Nakahama et al teach transformation of respiration deficient yeast. Nakahama teach that respiratory deficient strains of yeast transformed with expression plasmids of genes provide higher gene expression than their parent strains (i.e. non-respiratory deficient yeast) and that the gene expression is increased by rendering the yeast respiratory deficient (see abstract and column 2 lines 3141).

It would have been obvious to one of ordinary skill in the art at the time of the invention to use a respiratory deficient yeast for transformation and expression of genes in the method of screening of Bounaga et al as taught by Nakahama et al because Nakahama teach that respiratory deficient strains of yeast transformed with expression plasmids of genes provide higher gene expression that their parent strains and provide a higher amount of expressed protein.

Superti-furga et al is set forth supra. Superti-furga et al does not teach a method of screening wherein the transformed yeast is deficient in aspiration ability. Nakahama et al teach transformation of respiration deficient yeast. Nakahama teach that respiratory deficient strains of yeast transformed with expression plasmids of genes provide higher gene expression than their parent strains (i.e. non-respiratory deficient yeast) and that the gene expression is increased by rendering the yeast respiratory deficient (see abstract and column 2 lines 31-41).

It would have been obvious to one of ordinary skill in the art at the time of the invention to use a respiratory deficient yeast for transformation and expression of genes in the method of screening of Superti-furga et al as taught by Nakahama et al because Nakahama teach that respiratory deficient strains of yeast transformed with expression plasmids of genes provide higher gene expression that their parent strains and provide a higher amount of expressed protein.

Florio et al is set forth supra. Florio et al does not teach a method of screening wherein the transformed yeast is deficient in aspiration ability.

Nakahama et al teach transformation of respiration deficient yeast. Nakahama teach that respiratory deficient strains of yeast transformed with expression plasmids of genes provide higher gene expression than their parent strains (i.e. non-respiratory deficient yeast) and that the gene expression is increased by rendering the yeast respiratory deficient (see abstract and column 2 lines 31-41).

It would have been obvious to one of ordinary skill in the art at the time of the invention to use a respiratory deficient yeast for transformation and expression of genes in the method of screening of Florio et al as taught by Nakahama et al because Nakahama teach that respiratory deficient strains of yeast transformed with expression plasmids of genes provide higher gene expression that their parent strains and provide a higher amount of expressed protein.

Perkins et al is set forth supra. Perkins et al does not teach a method of screening wherein the transformed yeast is deficient in aspiration ability.
Nakahama et al teach transformation of respiration deficient yeast. Nakahama teach that respiratory deficient strains of yeast transformed with expression plasmids of genes provide higher gene expression than their parent strains (i.e. non-respiratory deficient yeast) and that the gene expression is increased by rendering the yeast respiratory deficient (see abstract and column 2 lines 31-41).

It would have been obvious to one of ordinary skill in the art at the time of the invention to use a respiratory deficient yeast for transformation and expression of genes in the method of screening of Perkins et al as taught by Nakahama et al because Nakahama teach that respiratory deficient strains of yeast transformed with expression plasmids of genes provide higher gene expression that their parent strains and provide a higher amount of expressed protein.

New Grounds of Rejection

Claim Rejections - 35 USC § 103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1, 19-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bounaga et al WO 01/20020 March 23, 2001 in view of Nakahama et al 1193 US Patent No. 5182195 and Naihe et al WO 02/68687 September 6, 2002.

The claims are drawn to

A method of screening a physiologically active substance, comprising the steps of:

a) contacting a test sample with a transformed yeast; capable of expressing a protein involved in proliferation or differentiation of cells or regulating cell cycles of a mammalian cell, wherein the transformed yeast is respiration ability deficient and show a change in the growth rate of said transformed yeast;

b) culturing said transformed yeast under conditions that result in expression of said protein and

c) measuring the growth rate of said cultured yeast, wherein the physiologically active substance is judged to be present in the test sample in a case where the growth of the yeast is lowered or improved in the presence of the test sample as compared to that in the absence of the test sample as a control (claim 1);

A method of screening for a physiologically active substance, comprising:

(a) culturing a test culture comprising a test physiologically active substance and a yeast transformed with a recombinant expression vector, wherein said transformed yeast is respiration deficient and has a sensitized growth rate due to the expression of a heterogeneous protein encoded by said vector, and wherein said protein controls the proliferation of mammalian cells or regulates the cell cycle of mammalian cells;
(b) measuring a growth state of said transformed yeast in said test culture;
(c) culturing a control culture of said transformed yeast;
(d) measuring a growth state of said control culture; and
(e) comparing the growth states of said test and control cultures; wherein said test physiologically active substance is judged to have physiological activity where the growth state of said transformed yeast in said test culture is lowered or improved as compared to the growth rate of said yeast in said control culture (claim 19), wherein said protein is a Tob family protein and or a Caf family protein (claim 20).

Bounaga et al teach a method for screening and identification of compounds or compositions useful as herbicides, growth regulators or fungicides comprising (1) addition of a compound or composition to be screened or identified to a culture or culture area of a yeast strain transformed with and expressing one or more plant or animal or human cell cycle control genes or mutants thereof as well as to a control yeast strain; and (2) determining the effect on the phenotype such as inhibition or stimulation of growth and/or cell division and/or changing cell shape and size of said transformed yeast compared to said control yeast (page 4 lines 1-9, page 7 line 21, page 12 lines 30-34). Bounaga et al teach that the transformed yeast expresses a cell cycle control gene resulting in growth arrest or growth acceleration (page 30 claims 7 and 8) and said cell cycle control gene is involved in regulation of cell cycle of a mammal (page 12 lines 30-34), for example, involved in control of entry (that is from GO/G1 phase) and progression through S phase of the cell cycle (page 5 lines 9-10) such as cyclin dependent kinases (CDK), cyclin dependent kinase inhibitor, cyclin A, D, E etc (page 5 line 1-9 and lines 10-34 and page 6 lines 1-9). Bounaga et al teach methods of testing effect of compounds or compositions on growth of yeast (page 15

lines 27-34) by measuring shape, size, number, growth rate, growth stimulation or growth inhibition, phenotype, turbidity (page 16 lines 4-13). Bounaga et al teach that the present invention includes the use of a recombinant vector comprising at least one polynucleic acid encoding at least part of a plant cell cycle control protein or a mutant thereof to transform yeast for the screening or identification of compounds or compositions which abolish, retard or stimulate plant growth. Said recombinant vector is a plasmid, more particularly a vector comprising a selectable marker and transcriptional control elements for the expression of said plant or animal/human cell cycle control polynucleic acids in yeast. Said plant or animal/human cell cycle control polynucleic acid is integrated into the yeast genome by random, non-homologous or homologous recombination (see pg. 13 lines 1-10).

However, Bounaga et al does not teach a method of screening wherein the transformed yeast is respiration deficient. Nakahama et al teach transformation of respiration deficient yeast. Nakahama teach that respiratory deficient strains of yeast transformed with expression plasmids of genes provide higher gene expression than their parent strains (i.e. non-respiratory deficient yeast) and that the gene expression is increased by rendering the yeast respiratory deficient (see abstract and column 2 lines 3141). Naihe et al teach wherein a protein is Tob family protein. Naihe et al teach that Tob protein manifest an inhibiting action on cell growth thus Naihe et al teach a protein that controls cell proliferation (see pg. 1 paragraph 3).

It would have been obvious to one of ordinary skill in the art at the time of the invention to use a respiratory deficient yeast for transformation and expression of genes in the method of screening of Bounaga et al as taught by Nakahama et al because Nakahama teach that respiratory deficient strains of yeast transformed with expression plasmids of genes provide higher gene expression that their parent strains and provide a higher amount of expressed protein. It would also have been obvious to one of ordinary skill in the art at the time of the invention to incorporate a Tob protein taught by Naihe et al in the method of because method of screening of Bounaga et al as taught by Nakahama et al because Naihe et al teach that Tob protein manifest an inhibiting action on cell growth thus Naihe et al teach a protein that controls cell proliferation.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 21-22 and 25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The claim is drawn to a vast genus of amino acids of SEQ ID NO:1, SEQ ID NO: 2, and SEQ ID NO: 4. To fulfill the written description requirements set forth under 35 USC § 112, first paragraph, the specification must describe at least a substantial number of the members of the claimed genus, or alternatively describe a representative member of the claimed genus, which shares a particularly defining feature common to at least a substantial number of the members of the claimed genus, which would enable the skilled artisan to immediately recognize and distinguish its members from others, so as to reasonably convey to the skilled artisan that Applicant has possession the claimed invention. To adequately describe the genus of amino acids of SEQ ID NO:1, SEQ ID NO: 2, and SEQ ID NO: 4, applicant must also give a functional limitation of which amino acids of SEQ ID NOs: 1, 2, and 4.

The specification, however, does not disclose distinguishing and identifying features of a representative member of the genus of the amino acids of SEQ ID NOs:1, 2, and 4 to which the claims are drawn, such as a correlation between structure of the

peptide and its recited function, so that the skilled artisan could immediately envision or recognize at least a substantial number of members of the claimed genus of antigens.

MPEP § 2163.02 states, "an objective standard for determining compliance with the written description requirement is, 'does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed". The courts have decided: The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the "written description" inquiry, whatever is now claimed. See Vas-Cath, Inc.'v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Federal Circuit, 1991). Furthermore, the written description provision of 35 USC § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993)and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, "'Written Description" Requirement (66 FR 1099-1111, January 5,2001) state, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (Id. at 1104).

The Guidelines further state, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus" (Id. at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus.

It is noted that applicant(s) have listed a sequence which is known in the prior art and which has a high percentage similarity to a claimed sequence. Absent factual evidence, a percentage sequence similarity of less than 100% is not deemed to reasonably support to one skilled in the art whether the biochemical activity of the claimed subject matter would be the same as that of such a similar known biomolecule. It is known for nucleic acids as well as proteins, for example, that even a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many instances, albeit not in all cases. The effect of these changes are largely unpredictable as to which one have significant effect versus not. Therefore, the citation of sequence similarity results in an unpredictable and therefore unreliable correspondence between the claimed biomolecule and the indicated similar biomolecule of known function and therefore lacks support regarding utility and/or enablement. Several publications document this unpredictability of the relationship between sequence and function, albeit that certain specific sequence may be found to be conserved over biomolecules of related function upon a significant amount of further research. See the following publications that support this unpredictability as noting certain conserved sequences in limited specific cases: Therefore, in accordance with the Guidelines, the description of amino acids is not deemed representative of the genus amino acids of SEQ ID NO:1, SEQ ID NO: 2, and SEQ ID NO: 4 of the claim invention thus the claim does not meet the written description requirement.

Conclusion

Status of the Claims

8. No claims are allowed.

Claims 1-5 and 19-22 and 25 are rejected.

Claims 23-24 and 26-28 objected to as being dependent on rejected claim.

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nina A. Archie whose telephone number is 571-272-9938. The examiner can normally be reached on Monday-Friday 8:30-5:00p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Nina A Archie
Examiner
GAU 1645
REM 3B31

MARK NAVARRO
PRIMARY EXAMINER